Different fever definitions and the rate of fever and neutropenia diagnosed in children with cancer: A retrospective two-center cohort study

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Abstract: BACKGROUND: The definition of fever, and thus fever and neutropenia (FN), varies between different pediatric oncology centers. Higher temperature limit should reduce FN rates, but may increase rates of FN with complications by delaying therapy. This study determined if different fever definitions are associated with different FN rates. PROCEDURE: Two pediatric oncology centers had used three fever definitions in 2004-2011: ear temperature 38.5°C persisting 2 hours (low definition); axillary temperature 38.5°C 2 hours or 39.0°C once (middle); and ear temperature 39.0°C once (high). Clinical information was retrospectively extracted from charts. FN rates were compared using mixed Poisson regression. RESULTS: In 521 pediatric patients with cancer, 783 FN were recorded during 6,009 months cumulative chemotherapy exposure time (501 years; rate, 0.13/month [95% CI, 0.12-0.14]), 124 of them with bacteremia (16%; 0.021/month [0.017-0.025]). In univariate analysis, the high versus low fever definition was associated with a lower FN rate (0.10/month [0.08-0.11] vs. 0.15/month [0.13-0.16]; rate ratio, 0.66 [0.45-0.97]; P = 0.036), the middle definition was intermediate (0.13/month [0.11-0.15]). This difference was not confirmed in multivariate analysis (rate ratio, 0.94 [0.67-1.33]; P = 0.74). The high versus low definition was not associated with an increased rate of FN with bacteremia (multivariate rate ratio, 1.39 [0.53-3.62]; P = 0.50). CONCLUSION: A higher fever definition was not associated with a lower FN rate, nor with an increased rate of FN with bacteremia. These may be false negative findings due to methodological limitations. These questions, with their potential impact on health-related quality of life, and on costs, need to be assessed in prospective studies. Pediatr Blood Cancer © 2012 Wiley Periodicals, Inc.

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Different Fever Definitions and the Rate of Fever and Neutropenia Diagnosed in Children With Cancer: A Retrospective Two-Center Cohort Study

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Background. The definition of fever, and thus fever and neutropenia (FN), varies between different pediatric oncology centers. Higher temperature limit should reduce FN rates, but may increase rates of FN with complications by delaying therapy. This study determined if different fever definitions are associated with different FN rates. ***Procedure.*** Two pediatric oncology centers had used three fever definitions in 2004–2011: ear temperature $\geq$38.5°C persisting $\geq$2 hours (low definition); axillary temperature $\geq$38.5°C $\geq$2 hours or $\geq$39.0°C once (middle); and ear temperature $\geq$39.0°C once (high). Clinical information was retrospectively extracted from charts. FN rates were compared using mixed Poisson regression. ***Results.*** In 521 pediatric patients with cancer, 783 FN were recorded during 6,009 months cumulative chemotherapy exposure time (501 years; rate, 0.13/month [95% CI, 0.12–0.14]), 124 of them with bacteremia (16%; 0.021/month [0.017–0.025]). In univariate analysis, the high versus low fever definition was associated with a lower FN rate (0.10/month [0.08–0.11] vs. 0.15/month [0.13–0.16]; rate ratio, 0.66 [0.45–0.97]; $P = 0.036$), the middle definition was intermediate (0.13/month [0.11–0.15]). This difference was not confirmed in multivariate analysis (rate ratio, 0.94 [0.67–1.33]; $P = 0.74$). The high versus low definition was not associated with an increased rate of FN with bacteremia (multivariate rate ratio, 1.39 [0.53–3.62]; $P = 0.50$). ***Conclusion.*** A higher fever definition was not associated with a lower FN rate, nor with an increased rate of FN with bacteremia. These may be false negative findings due to methodological limitations. These questions, with their potential impact on health-related quality of life, and on costs, need to be assessed in prospective studies. Pediatr Blood Cancer 2013;60:799–805. © 2012 Wiley Periodicals, Inc.

Key words: chemotherapy; fever definition; fever in neutropenia; infection; pediatric oncology

INTRODUCTION

Fever and neutropenia (FN), specifically fever in severe chemotherapy-induced neutropenia, is the most frequent potentially lethal complication of chemotherapy in pediatric and adult patients with cancer [1]. The current management with emergency hospitalization and empirical administration of intravenous broad-spectrum antibiotics has decreased mortality to below 1% in pediatric FN [2]. The two criteria defining FN directly influence whether the diagnosis of FN is made or not. These criteria thus have important implications on individual patient management, treatment-related mortality, and costs in pediatric oncology [3]. The first criterion, severe neutropenia, is quite uniformly defined and applied in pediatric oncology practice, as an absolute neutrophil count $\leq$0.5 G/L or $\leq$1.0 G/L and expected to rapidly decline [1]. The second criterion, however, the temperature limit defining fever, relevantly varies between different pediatric oncology centers, even within the same country [4]. The temperature limit clinically applied varied from 37.5 to 39.0°C in 21 centers in the United Kingdom in 2005 [5], and from 38.0 to 39.0°C in 9 centers in Switzerland in 2012 (unpublished data). The temperature limit reported in 24 recently reviewed [6] original research articles on pediatric FN published in 2010 and 2011 varied as well from 37.5 to 39.0°C (Fig. 1). Current guidelines on the management of pediatric FN, developed by an international panel of 21 experts, do not discuss a temperature limit defining fever [7].

By definition, the application of higher temperature limits defining FN should decrease the rate of FN diagnosed, but might increase the rate of FN with complicated bacterial infections because of delayed diagnosis and start of empirical antimicrobial therapy. We do not know of any published results of retrospective or prospective studies on such associations.

This study aimed to explore if different temperature limits defining fever were associated with differences in the rate of FN, and of FN with bacteremia, in pediatric patients with cancer.

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METHODS

Study Design and Patients

This retrospective cohort study was conducted in two pediatric oncology centers in Switzerland. All children and adolescents up to 17 years diagnosed with a malignancy requiring chemotherapy between January 1, 2004 and June 30, 2011 were eligible for this study. Patients were identified through the centers' patient lists and the Swiss Childhood Cancer Registry. Information about chemotherapy, FN episodes, and 12 clinical characteristics potentially associated with FN (see Table I) [1,8] were extracted from patient charts by the first author (PB). This study was approved by the institutional review board with waiver of informed consent.

Definitions

Severe neutropenia was always defined as absolute neutrophil count $\leq$0.5 G/L [1,2]. Different definitions for fever were used. In center 1, fever was defined throughout the entire study period as an ear temperature $\geq$38.5°C persisting for $\geq$2 hours, without limit for a single temperature (low definition). In center 2, fever was

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Conflict of interest: Nothing to declare.

The results of this study have been presented in part at the 44th Congress of the International Society of Pediatric Oncology, London, UK, October 5–8, 2012.

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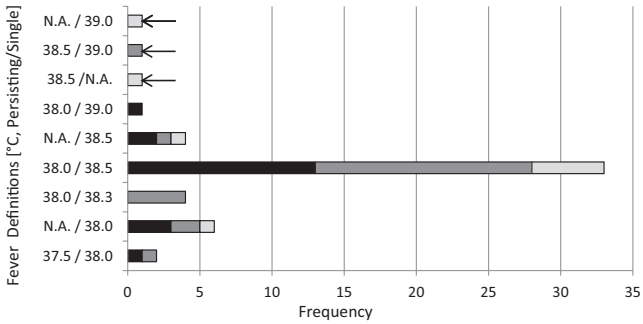

Fig. 1. Different fever definitions used clinically and in research on FN. Temperature limits are indicated as temperature persisting for 1–4 hours/single temperature (NA, not applicable). The bars indicate frequencies, differentiated into clinically used definitions in 21 pediatric oncology centers in the United Kingdom 2005 (black) [5] and 9 centers in Switzerland 2012 (light gray), and definitions used in 24 research articles published in 2010 and 2011 from different countries (dark gray) [6]. The arrows indicate the three temperature limits studied here.

defined from January 1, 2004 to July 8, 2007 as an axillary temperature $\geq$38.5°C persisting for $\geq$2 hours, or a single axillary temperature $\geq$39°C (middle) [8], and from July 9, 2007 to the end of the study period as a single ear temperature $\geq$39°C (high). The maximum temperature measured at home or in the emergency department was used. If clinically indicated, the attending physicians in both centers were free to diagnose FN and to treat patients accordingly even if these temperature limits had not been reached.

FN was differentiated into episodes with and without bacteremia as a clinically important and well-defined complication. Aerobic and anaerobic blood cultures were taken at presentation with FN before starting antimicrobial therapy. Subsequent blood cultures were taken if patients remained febrile, or when they had shaking chills. Blood cultures were drawn from each lumen of existing central venous catheter, where applicable, or from peripheral venous lines. Peripheral and central cultures were not performed in parallel. Bacteremia was defined as at least one positive blood culture, irrespective of the pathogen detected, using a qualitative automated culture system (BacT/ALERT, bioMérieux, Geneva, Switzerland; or BACTEC, Becton Dickinson, Basel, Switzerland) [2,9].

Chemotherapy was classified into four levels of myelosuppressive intensity according to the expected duration of severe neutropenia: level 1, no severe neutropenia expected; levels 2 versus 3, $\leq$10 versus >10 days severe neutropenia expected; and level 4, myeloablative chemotherapy requiring autologous hematopoietic stem cell rescue [10,11]. Myeloablative chemotherapy preceding allogeneic bone marrow transplantation was excluded from analysis. Chemotherapy exposure time was defined as the cumulative duration of chemotherapy plus 3 weeks accounting for neutropenia developing after cessation of chemotherapy [1,8]. Because characteristics related to therapy and course of disease (e.g., chemotherapy intensity or relapse) could change over time, different observation periods per patient could be defined. During each observation period, all characteristics potentially associated with FN had to remain constant [8].

Clinical Management of Fever in Neutropenia

During the entire study period, routine management for patients with cancer presenting with FN was emergency hospitalization and empirical broad-spectrum intravenous antimicrobial therapy. The first-line therapy was meropenem monotherapy in center 1, and a combination of ceftriaxone plus amikacin in center 2 [8].

Measures to Increase Data Quality

Three measures were used in order to compensate for the drawbacks of the retrospective study design. First, the centers' patient lists were supplemented by information from the Swiss Childhood Cancer Registry in order to maximize patient coverage. Second, information on FN episodes from the prospective SPOG 2003 FN study [2,9], which had recruited patients from 2004 to 2007 in both centers, was used in order to maximize coverage of FN episodes. This information was as well used to calculate an improved estimate of the FN rate. Third, the senior author (RAA) made a plausibility check of data on chemotherapy intensity and duration.

Power Analysis

The second hypothesis, that is, that a higher fever definition may be associated with a higher rate of FN with bacteremia, was used for a one-sided power analysis on Poisson distributed data [12]. In order to reach 80% power, with alpha set at 5%, to detect a 50% increase of the FN rate with bacteremia (standardized difference, 0.5), 125 FN episodes with bacteremia were needed. Assuming a proportion of FN with bacteremia of 20% [1,2], this corresponded to 625 FN episodes in total. With an estimated cumulative annual incidence of 85 FN episodes in the two centers, the study had to cover 7.5 years, that is, January 2004 to June 2011. For FN the sample size of 625 FN episodes corresponds to around 90% power to detect a 25% increase of the FN rate (standardized difference, 0.25).

Statistical Analysis

Because of non-normally distributed data, medians, ranges, and interquartile ranges (IQR) were calculated for continuously measured variables. FN Poisson rates were calculated per month, together with their unconditional exact 95% confidence intervals (CI).

Associations of characteristics potentially associated with FN, and with FN with bacteremia, were assessed using univariate and multivariate mixed Poisson regression, with chemotherapy exposure time as rate multiplier, and with a random intercept per patient [8,13]. For multivariate analysis, all characteristics statistically significant in univariate analysis, plus fever definition as the main variable of interest, were included into the model [12]. The characteristics center and year of chemotherapy start were not included in the multivariate model because of the important collinearity with fever definition.

P-values below 0.05 were considered significant. All analyses were performed using R 2.14.0 (R Foundation for Statistical Computing, Vienna, Austria). Specifically, the *glmmPQL* procedure was used for mixed Poisson regression [14].

TABLE I. Characteristics Associated With FN, Univariate Analysis

Characteristics	Rate of FN episodes			Univariate analysis	
	Episodes	Time[a]	Rate (95% CI)	Rate ratio (95% CI)	*P*-value
Patient- and center-related characteristics					
Pediatric oncology center					
Center 1	481	3,274	0.15 (0.13–0.16)	1.33 (0.98–1.81)	0.070
Center 2	302	2,734	0.11 (0.10–0.12)	Reference	—
Fever definition					
Low (38.5/NA °C, center 1)	481	3,274	0.15 (0.13–0.16)	Reference	—
Middle (38.5/39.0°C, center 2)	141	1,080	0.13 (0.11–0.15)	0.89 (0.59–1.33)	0.57
High (NA/39.0°C, center 2)	161	1,654	0.10 (0.08–0.11)	0.66 (0.45–0.97)	0.036
Sex					
Male	413	3,591	0.12 (0.10–0.13)	Reference	—
Female	370	2,417	0.15 (0.14–0.17)	1.33 (0.99–1.79)	0.060
Age at diagnosis					
<4 years	268	2,025	0.13 (0.12–0.15)	Reference	—
4.00–7.99 years	214	1,665	0.13 (0.11–0.15)	0.97 (0.66–1.42)	0.88
8.00–11.99 years	132	1,049	0.13 (0.11–0.15)	0.95 (0.61–1.48)	0.82
≥12 years	169	1,270	0.13 (0.11–0.15)	1.01 (0.67–1.52)	0.98
Disease-related characteristics					
Diagnostic group					
Acute lymphoblastic leukemia	314	3,021	0.10 (0.09–0.12)	Reference	—
Acute myeloid leukemia	110	406	0.27 (0.22–0.33)	2.61 (1.65–4.11)	<0.001
Hodgkin lymphoma	10	193	0.05 (0.02–0.10)	0.50 (0.13–1.86)	0.30
Non-Hodgkin lymphoma	50	272	0.18 (0.14–0.24)	1.77 (0.95–3.31)	0.074
Solid tumor outside the CNS	226	1,358	0.17 (0.15–0.19)	1.60 (1.12–2.29)	0.010
Tumor of the CNS	73	759	0.10 (0.08–0.12)	0.93 (0.54–1.58)	0.78
Relapse/second malignancy					
Unrelapsed first malignancy	692	5,512	0.13 (0.12–0.14)	Reference	—
Relapse or second malignancy	91	496	0.18 (0.15–0.23)	1.46 (0.91–2.33)	0.11
Characteristics of therapy and course					
Myelosuppressive intensity of chemotherapy[b]					
1: no severe neutropenia expected	104	2,226	0.05 (0.04–0.06)	Reference	—
2: severe neutropenia ≤10 days expected	519	3,296	0.16 (0.14–0.17)	3.37 (2.28–4.98)	<0.001
3: severe neutropenia >10 days expected	140	441	0.32 (0.27–0.37)	6.79 (4.25–10.9)	<0.001
4: myeloablative chemotherapy	20	46	0.44 (0.27–0.68)	9.37 (3.86–22.7)	<0.001
Year of chemotherapy start					
2004/2005	173	978	0.18 (0.15–0.21)	1.77 (1.10–2.85)	0.018
2006/2007	214	1,558	0.14 (0.12–0.16)	1.38 (0.88–2.16)	0.17
2008/2009	244	1,949	0.13 (0.11–0.14)	1.26 (0.81–1.95)	0.31
2010/2011	152	1,524	0.10 (0.08–0.12)	Reference	—
Central venous access device					
None implanted	79	905	0.09 (0.07–0.11)	Reference	—
Central venous access device implanted	704	5,104	0.14 (0.13–0.15)	1.58 (0.96–2.61)	0.075
Bone marrow involvement					
No	664	5,564	0.12 (0.11–0.13)	Reference	—
Yes (≥25% malignant cells)	119	444	0.27 (0.22–0.32)	2.24 (1.50–3.36)	<0.001
Prior episodes of FN					
No	319	2,679	0.12 (0.11–0.13)	Reference	—
Yes	464	3,329	0.14 (0.13–0.15)	1.17 (0.86–1.60)	0.32
Prior episodes of FN with bacteremia					
No	658	4,948	0.13 (0.12–0.14)	Reference	—
Yes	125	1,060	0.12 (0.10–0.14)	0.89 (0.59–1.33)	0.56

FN, fever in severe chemotherapy-induced neutropenia; CNS, central nervous system; NA, not applicable. [a]Cumulative time of chemotherapy exposure in months; [b]See Refs. 10,11.

RESULTS

Patients

A total of 521 patients were studied here, 310 (60%) treated in center 1, and 211 (40%) in center 2, and 217 (42%) were female. The median age at diagnosis of malignancy was 5.9 years (range, 2 days to 16.8 years; IQR, 2.5–11.6 years). Diagnoses were acute lymphoblastic leukemia (ALL) in 161 (31%) patients, acute myeloid leukemia (AML) in 36 (7%), Hodgkin lymphoma in 41 (8%), Non-Hodgkin lymphoma in 33 (6%), solid tumors outside the

central nervous system (CNS) in 170 (33%), and CNS tumors in 80 (15%). 42 (8%) patients had a relapse or a second malignancy.

Chemotherapy

The cumulative chemotherapy exposure time in these 521 patients was 182,886 days (6,009 months, 501 years). The myelosuppressive intensity was 1 during 2,226 months, 2 during 3,296 months, 3 during 441 months, and 4 during 46 months. The entire chemotherapy exposure time was recorded in 1,709 observation periods (median per patient, 3; range, 1–12; IQR, 2–4) with a median duration of 58 days (range, 1–731; IQR, 20–147).

Episodes of Fever in Neutropenia

During the cumulative chemotherapy exposure time of 6,009 months, 783 FN episodes were recorded (rate, 0.13 episodes per month; 95% CI, 0.12–0.14). Bacteremia was detected in 124 (16%) of these 783 FN episodes (rate, 0.021 per month; 95% CI, 0.017–0.025). Of the 521 patients, 302 (58%) had at least one FN episode (median per patient, 1; IQR, 0–2; range, 0–11), and 92 (18%) had at least one FN episode with bacteremia (median per patient, 0; range, 0–4). Death was considered to be caused by infection in five (0.6%) patients with FN episodes, four of them with bacteremia, and one with rhinocerebral mucormycosis [15].

An improved estimate of the FN rate was calculated based on information from the second measure to increase data quality. In the patients participating in the prospective SPOG 2003 FN study between 2004 and 2007, 52 (21%) of the corresponding 247 FN episodes had been reported only in SPOG 2003 FN, but were not detected by retrospective chart review here. This proportion was comparable between centers (18% vs. 25%). Extrapolating this proportion to all patients in the entire time studied here led to an increased estimate of 939 (plus 20%) instead of 783 FN episodes in 6,009 months cumulative chemotherapy exposure time. This corresponds to an increased rate estimate of 0.16 FN per month, instead of 0.13.

Fever Definitions and the Risk to Develop FN

The rate of FN episodes per month was 0.15 (95% CI, 0.13–0.16) for the low fever definition. It was 0.13 (95% CI, 0.11–0.15) for the middle, and 0.10 (95% CI, 0.08–0.11) for the high definition (Table I).

In univariate analysis, the high versus low fever definition was associated with a significantly lower FN rate (rate ratio, 0.66; 95% CI, 0.45–0.97; $P = 0.036$; Table I). Four of the remaining 11 characteristics, that is, diagnostic group (AML and solid tumor outside the CNS, respectively, vs. ALL), chemotherapy intensity (levels 2, 3, and 4 vs. level 1), bone marrow involvement, and the time period of chemotherapy start (2004/05 vs. 2010/11) were all significantly associated with an increased FN rate. The other seven characteristics, namely center, sex, age at diagnosis, relapse status, central venous access device, prior episodes of FN, and prior episodes of FN with bacteremia, were not significantly associated with the FN rate.

In multivariate analysis, when corrected for the three variables diagnostic group, chemotherapy intensity, and bone marrow involvement, fever definition was not significantly associated any more with the FN rate (high vs. low rate ratio, 0.94; 95% CI, 0.67–1.33; $P = 0.74$; Table II). Diagnostic group (Hodgkin lymphoma and CNS tumor, respectively, vs. ALL), and chemotherapy intensity (levels 2, 3, and 4 vs. level 1), were significantly and independently associated with the FN rate (Table II). Nearly the entire variance was due to within-patient variance ($\tau = 0.000129$, $\sigma = 1.85$).

Fever Definitions and the Risk to Develop FN With Bacteremia

The rate of FN episodes with bacteremia per month was 0.022 (95% CI, 0.017–0.028) for the low fever definition. It was 0.022 (95% CI, 0.014–0.033) for the middle, and 0.017 (95% CI, 0.011–0.024) for the high definition (Table III).

In univariate analysis, the high versus low fever definition was not significantly associated with the rate of FN with bacteremia

TABLE II. Characteristics Associated With FN, Multivariate Analysis

Characteristics	Rate ratio (95% CI)	*P*-value
Fever definition		
Low (38.5/NA °C, center 1)	Reference	—
Middle (38.5/39.0°C, center 2)	1.05 (0.73–1.49)	0.80
High (NA/39.0°C, center 2)	0.94 (0.67–1.33)	0.74
Diagnostic group		
Acute lymphoblastic leukemia	Reference	—
Acute myeloid leukemia	0.53 (0.22–1.26)	0.16
Hodgkin lymphoma	0.26 (0.08–0.84)	0.025
Non-Hodgkin lymphoma	0.74 (0.38–1.43)	0.37
Solid tumor outside the CNS	0.79 (0.55–1.15)	0.22
Tumor of the CNS	0.50 (0.30–0.82)	0.007
Myelosuppressive intensity of chemotherapy[a]		
1: no severe neutropenia expected	Reference	—
2: severe neutropenia ≤10 days expected	4.14 (2.66–6.44)	<0.001
3: severe neutropenia >10 days expected	10.2 (4.36–23.8)	<0.001
4: myeloablative chemotherapy	13.6 (5.24–35.0)	<0.001
Bone marrow involvement	1.26 (0.81–1.96)	0.30

FN, fever in severe chemotherapy-induced neutropenia; CNS, central nervous system; NA, not applicable. [a]see Refs. 10,11.

TABLE III. Characteristics Associated With FN With Bacteremia, Univariate Analysis

Characteristics	Rate of FN episodes			Univariate analysis	
	Episodes	Time[a]	Rate (95% CI)	Rate ratio (95% CI)	*P*-value
Patient- and center-related characteristics					
Pediatric oncology center					
Center 1	72	3,274	0.022 (0.017–0.028)	1.16 (0.46–2.88)	0.76
Center 2	52	2,734	0.019 (0.014–0.025)	Reference	—
Fever definition					
Low (38.5/NA °C, center 1)	72	3,274	0.022 (0.017–0.028)	Reference	—
Middle (38.5/39.0°C, center 2)	24	1,080	0.022 (0.014–0.033)	1.01 (0.31–3.32)	0.99
High (NA/39.0°C, center 2)	28	1,654	0.017 (0.011–0.024)	0.77 (0.25–2.37)	0.65
Sex					
Male	64	3,591	0.018 (0.014–0.023)	Reference	—
Female	60	2,417	0.025 (0.019–0.032)	1.39 (0.58–3.36)	0.46
Age at diagnosis					
<4 years	50	2,025	0.025 (0.018–0.033)	Reference	—
4.00–7.99 years	25	1,665	0.015 (0.010–0.022)	0.61 (0.18–2.06)	0.42
8.00–11.99 years	13	1,049	0.012 (0.007–0.021)	0.50 (0.11–2.36)	0.38
≥ 12 years	36	1,270	0.028 (0.020–0.039)	1.15 (0.39–3.41)	0.80
Disease-related characteristics					
Diagnostic group					
Acute lymphoblastic leukemia	55	3,021	0.018 (0.014–0.024)	Reference	—
Acute myeloid leukemia	35	406	0.086 (0.060–0.120)	5.04 (1.86–13.6)	0.001
Hodgkin lymphoma	0	193	0.000 (0.000–0.019)	—	—
Non-Hodgkin lymphoma	6	272	0.022 (0.008–0.048)	1.29 (0.18–9.33)	0.80
Solid tumor outside the CNS	22	1,358	0.016 (0.010–0.025)	0.95 (0.30–3.02)	0.93
Tumor of the CNS	6	759	0.008 (0.003–0.017)	0.46 (0.06–3.34)	0.44
Relapse/second malignancy					
Unrelapsed first malignancy	110	5,512	0.020 (0.016–0.024)	Reference	—
Relapse or second malignancy	14	496	0.028 (0.015–0.047)	1.41 (0.35–5.78)	0.63
Characteristics of therapy and course					
Myelosuppressive intensity of chemotherapy[b]					
1: no severe neutropenia expected	14	2,226	0.006 (0.003–0.011)	Reference	—
2: severe neutropenia $\leq$10 days expected	68	3,296	0.021 (0.016–0.026)	3.28 (0.96–11.1)	0.057
3: severe neutropenia $>$10 days expected	39	441	0.088 (0.063–0.121)	14.1 (3.83–51.5)	$<$0.001
4: myeloablative chemotherapy	3	46	0.066 (0.014–0.192)	10.4 (0.74–148)	0.083
Year of chemotherapy start					
2004/2005	33	978	0.034 (0.023–0.047)	2.06 (0.53–7.94)	0.29
2006/2007	29	1,558	0.019 (0.012–0.027)	1.13 (0.28–4.55)	0.37
2008/2009	37	1,949	0.019 (0.013–0.026)	1.16 (0.31–4.33)	0.36
2010/2011	25	1,524	0.016 (0.011–0.024)	Reference	—
Central venous access device					
None implanted	17	905	0.019 (0.011–0.030)	Reference	—
Central venous access device implanted	107	5,104	0.021 (0.017–0.025)	1.12 (0.31–4.08)	0.87
Bone marrow involvement					
No	86	5,564	0.015 (0.012–0.019)	Reference	—
Yes ($\geq$25% malignant cells)	38	444	0.086 (0.061–0.117)	5.53 (2.12–14.4)	$<$0.001
Prior episodes of FN					
No	51	2,679	0.019 (0.014–0.025)	Reference	—
Yes	73	3,329	0.022 (0.017–0.028)	1.15 (0.46–2.90)	0.76
Prior episodes of FN with bacteremia					
No	93	4,948	0.019 (0.015–0.023)	Reference	—
Yes	31	1,060	0.029 (0.020–0.042)	1.56 (0.54–4.50)	0.41

FN, fever in severe chemotherapy-induced neutropenia; CNS, central nervous system; NA, not applicable. [a]Cumulative time of chemotherapy exposure in months; [b]See Refs. 10,11.

(rate ratio, 0.77; 95% CI, 0.25–2.37; $P = 0.65$; Table III). Three of the remaining 11 characteristics, that is, diagnostic group (AML vs. ALL), chemotherapy intensity (level 3 vs. level 1), and bone marrow involvement were all significantly associated with an increased rate of FN with bacteremia, while the other eight characteristics were not.

In multivariate analysis, when corrected for the three variables diagnostic group, chemotherapy intensity, and bone marrow involvement, fever definition was again not significantly associated with the rate of FN with bacteremia (high vs. low rate ratio, 1.39; 95% CI, 0.53–3.62; $P = 0.50$; Table IV). Neither diagnostic group nor bone marrow involvement was associated with the

TABLE IV. Characteristics Associated With FN With Bacteremia, Multivariate Analysis

Characteristics	Rate ratio (95% CI)	*P*-value
Fever definition		
Low (38.5/NA °C, center 1)	Reference	—
Middle (38.5/39.0°C, center 2)	1.42 (0.54–3.76)	0.48
High (NA/39.0°C, center 2)	1.39 (0.53–3.62)	0.50
Diagnostic group		
Acute lymphoblastic leukemia	Reference	—
Acute myeloid leukemia	0.82 (0.08–8.39)	0.87
Hodgkin lymphoma	—[a]	—[a]
Non-Hodgkin lymphoma	0.65 (0.09–4.69)	0.67
Solid tumor outside the CNS	0.56 (0.18–1.73)	0.32
Tumor of the CNS	0.29 (0.05–1.72)	0.17
Myelosuppressive intensity of chemotherapy[b]		
1: no severe neutropenia expected	Reference	—
2: severe neutropenia $\leq$10 days expected	4.58 (1.29–16.3)	0.019
3: severe neutropenia $>$10 days expected	12.2 (1.10–135)	0.042
4: myeloablative chemotherapy	24.9 (1.63–382)	0.021
Bone marrow involvement	2.45 (0.91–6.63)	0.077

FN, fever in severe chemotherapy-induced neutropenia; NA, not applicable. [a]No FN with bacteremia in patients with Hodgkin lymphoma; [b]See Refs. 10,11.

rate of FN with bacteremia independently from chemotherapy intensity (Table IV). Nearly the entire variance was due to within-patient variance ($\tau = 0.000307$, $\sigma = 2.03$).

DISCUSSION

There is no consensus on how to define fever, and thus FN, in pediatric oncology. This is the first study to assess the association between different fever definitions and the rate of diagnosis of FN. In this retrospective two-center study in pediatric patients with cancer, a higher temperature limit defining fever was not associated with a reduced rate of FN diagnosed during chemotherapy. A significant reduction of about one-third of the FN rate was associated with the high versus low definition of fever, that is, a single temperature of $\geq$39.0°C versus a temperature $\geq$38.5°C persisting for $\geq$2 hours, only in univariate analysis (Table I). When corrected for other FN risk factors in multivariate analysis, this reduction was not confirmed, and the FN rates in the three fever definitions studied were nearly equal, with quite narrow 95% CI (Table II).

This finding would implicate that all children with a temperature $\geq$38.5°C will reach as well a temperature $\geq$39.0°C, which contradicts clinical experience. We do think, however, that this negative and counterintuitive result is due to three methodological limitations of this study: First, the three temperature limits defining fever studied here were all in a narrow range at the uppermost border of the spectrum of temperatures reported (Fig. 1). This may lead to false negative results. Comparing temperature limits from opposite ends of the spectrum might increase the power to detect existing differences. Second, the different fever definitions were not independent from the centers: The low definition was only implemented in center 1, while the middle and the high definition were only implemented in center 2. Differences in the distribution of cancer diagnoses, in the proportion of FN diagnoses made clinically when the temperature limit defining fever was not reached, in chemotherapy, or in supportive therapy might systematically influence FN rates between centers besides fever definitions, allowing for important interaction effects. The temperature limits used clinically could not be reliably assessed in this retrospective study. It was not possible to directly estimate these interaction effects, but at least center itself was not associated with the FN rates. Third, the middle fever definition relied on axillary temperature measurements, while ear temperature measurements were used for the low and the high definitions. Compared to ear temperature, measured by infrared tympanic thermometry, axillary measurements are known to less reliably reflect core temperature, and to systematically result in lower findings by around 0.6°C [16]. This may have reduced the differences in core temperature between different definitions. Specifically, this may have impaired those comparisons which included the middle definition, but not comparisons between the high and the low definitions.

Furthermore, the rates of FN with bacteremia were not significantly different in the three fever definitions studied in univariate or multivariate analysis (Tables III and IV). Though the corresponding 95% CI were quite wide, a clinically relevant increase of 50% of the FN rate with bacteremia would have been detected with 80% power according to the results of the power analysis.

Wide and clinically relevant variations in fever definitions are known in pediatric oncology [5], and these variations have a potentially large impact on individual patient management, mortality associated with FN, and costs [3]. Despite this, we do not know of any published results of research on the topic of this study. A comparison of its main results with those of other research groups is thus not possible.

Regarding secondary results, the FN rate of 0.13 per month of chemotherapy found here was comparable to the rate of 0.12 per month (1.48 per year) reported for the period from 1993 to 2004 in center 2 [8]. The proportion of FN episodes with bacteremia was 16% and thus within the range of 10–24% reported earlier [8,9,17–19]. The characteristics associated with FN with or without bacteremia found here, that is, AML diagnosis, higher intensity of chemotherapy, and bone marrow involvement, are all well-known risk factors for FN [1]. Interestingly, the finding of prior episodes of FN as an independent risk factor for FN and FN with bacteremia, reported from center 2 before [8], could not be replicated here.

Strengths of this study include its two-center design; its large size, with 521 patients representing the entire spectrum of pediatric malignancies, with a cumulative chemotherapy exposure time of 501 years, and with 783 FN, 124 of them FN with bacteremia; and the use of mixed Poisson regression as a powerful tool to analyze the specific kind of data studied. In addition to the three methodological limitations discussed above, the retrospective design of this study entails the risk of missing patients, plus missing and incorrect data. Three measures to increase data quality were used to minimize these problems.

In conclusion, a higher temperature limit defining fever was not associated with a reduced rate of FN diagnosed during chemotherapy in this study. Furthermore, a higher temperature limit was not associated with an increased rate of FN with bacteremia. The counterintuitive negative finding regarding the FN rate may well be a false negative finding due to methodological limitations. These might be overcome in adequately designed prospective studies on higher versus lower temperature limits defining fever and thus FN. If future research could show that a higher temperature limit is both efficacious, by reducing the rate of FN diagnosis, and safe, by not relevantly increasing the rate of FN with complications such as bacteremia, this would have an important impact on health-related quality of life in pediatric patients with cancer, and on costs.

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